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# Schizotypy and brain structure: a voxel-based morphometry study

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**Background.** Schizotypy is conceptualized as a subclinical manifestation of the same underlying biological factors that give rise to schizophrenia and other schizophrenia spectrum disorders. Individuals with psychometric schizotypy (PS) experience subthreshold psychotic signs and can be psychometrically identified among the general population. Previous research using magnetic resonance imaging (MRI) has shown gray-matter volume (GMV) abnormalities in chronic schizophrenia, in subjects with an at-risk mental state (ARMS) and in individuals with schizotypal personality disorder (SPD). However, to date, no studies have investigated the neuroanatomical correlates of PS.

**Method.** Six hundred first- and second-year university students completed the Community Assessment of Psychic Experiences (CAPE), a self-report instrument on psychosis proneness measuring attenuated positive psychotic experiences. A total of 38 subjects with high and low PS were identified and subsequently scanned with MRI. Voxel-based morphometry (VBM) was applied to examine GMV differences between subjects with high and low positive PS.

**Results.** Subjects with high positive PS showed larger global volumes compared to subjects with low PS, and larger regional volumes in the medial posterior cingulate cortex (PCC) and the precuneus. There were no regions where GMV was greater in low than in high positive PS subjects.

**Conclusions.** These regions, the PCC and precuneus, have also been sites of volumetric differences in MRI studies of ARMS subjects and schizophrenia, suggesting that psychotic or psychotic-like experiences may have common neuroanatomical correlates across schizophrenia spectrum disorders.

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**Key words:** Gray matter, MRI, schizophrenia, schizotypy, voxel-based morphometry.

## Introduction

Structural neuroimaging studies have confirmed the presence of neuroanatomical abnormalities in schizophrenia (Wright *et al.* 2000). The most consistent findings are reductions in medial temporal and prefrontal regions, superior temporal gyri, parietal areas and subcortical regions, together with ventricular enlargement (Shenton *et al.* 2001). Previous studies have also reported that alterations in brain morphology are correlated with positive psychotic symptoms in schizophrenia (Young *et al.* 1991; Flaum *et al.* 1995; Suzuki *et al.* 2005a), particularly in the case of auditory hallucinations (see Allen *et al.* 2008 for review).

Subjects with an at-risk mental state (ARMS; Yung *et al.* 1998) show subthreshold psychotic symptoms, although only a proportion of them will ultimately progress to psychosis (McGorry & Singh, 1998; Yung *et al.* 2003). Magnetic resonance imaging (MRI) scanning of the brain in ARMS subjects has shown gray-matter volume (GMV) deficits compared to healthy controls, which overall do not seem to differ significantly from known deficits in schizophrenia (Pantelis *et al.* 2003; Velakoulis *et al.* 2006; Borgwardt *et al.* 2007b). Abnormalities have been found mainly in the medial temporal lobe (Lawrie *et al.* 1999; Pantelis *et al.* 2003; Velakoulis *et al.* 2006; Meisenzhal *et al.* 2008), superior temporal gyrus (Job *et al.* 2005; Borgwardt *et al.* 2007b; Meisenzhal *et al.* 2008), prefrontal cortex (Pantelis *et al.* 2003; Meisenzhal *et al.* 2008), cerebellum (Pantelis *et al.* 2003; Job *et al.* 2005), anterior cingulate gyrus (Pantelis *et al.* 2003; Borgwardt *et al.* 2008b; Fornito *et al.* 2008), posterior midline structures

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(Pantelis *et al.* 2003; Borgwardt *et al.* 2007*a,b*) and the insula lobe (Pantelis *et al.* 2003; Borgwardt *et al.* 2007*b*, 2008*a*). Notably, not only decreases but also increases in GMV have been observed (Pantelis *et al.* 2003; Shin *et al.* 2005; Borgwardt *et al.* 2007*a*). Taken together, these studies suggest that some anatomical abnormalities are present before illness onset, presumably independent of outcome.

Nevertheless, the neuroanatomical correlates of the distinctive positive psychotic symptoms often present in these populations remain poorly understood. Psychotic experiences are not encountered exclusively as part of a fully developed psychotic disorder or in high-risk subjects, as they may also be found in schizotypal personality disorder (SPD; APA, 1994) and in healthy individuals who can be psychometrically identified from the general population (Chapman *et al.* 1994). The few available neuroanatomical studies in SPD thus far align well with studies on schizophrenia and ARMS patients reporting general structural brain abnormalities compared to controls. These include the temporal lobe (Dickey *et al.* 1999; Downhill *et al.* 2001; Kawasaki *et al.* 2004; Suzuki *et al.* 2005*b*), inferior frontal gyrus and insula (Kawasaki *et al.* 2004) and the thalamic pulvinar nucleus (Byne *et al.* 2001). In addition, the prefrontal cortex was implicated in one investigation (Raine *et al.* 1992), although later studies failed to replicate this finding (Raine *et al.* 2002; Siever *et al.* 2002; Kawasaki *et al.* 2004; Suzuki *et al.* 2005*b*; Zhou *et al.* 2007), and further evidence suggests that this region might instead be involved in transition (Kawasaki *et al.* 2004; Suzuki *et al.* 2005*b*).

Epidemiological research has found a prevalence of 17.5% of any type of positive psychotic symptoms in the general population (Van Os *et al.* 2000), supporting the notion that psychometric schizotypy (PS) represents a dimensional trait, ranging from 'normality' to clinical cases of psychosis (Strauss, 1969). This is in agreement with continuity models of psychosis proneness, which understand such schizotypal features as part of the normal diversity of personality expression found in healthy individuals, although these features entail a cognitive vulnerability that predisposes towards psychosis (Chapman & Chapman, 1980). Hence, MRI findings in these subjects could inform the pathophysiology of psychotic-like experiences without the confounding effects of illness chronicity or medication. To date, however, no studies have investigated the brain volumetric characteristics of subjects with positive PS.

The aim of the present study was to compare GMV in people with high and low positive PS using voxel-based morphometry (VBM). VBM has been used successfully in prior research to ascertain brain morphology in patients with schizophrenia (Wright *et al.*

1999) and also in ARMS (Borgwardt *et al.* 2007*a,b*; Meisenzahl *et al.* 2008) and SPD subjects (Kawasaki *et al.* 2004). Based on the findings in these previous studies, we tested the hypothesis that individuals with high and low positive PS scores would show volumetric differences in the inferior frontal, insular, cingulate, medial and lateral temporal, and parietal cortex. We further hypothesized that gray-matter deficits in subjects with high levels of positive schizotypy would be qualitatively similar to those in ARMS or SPD subjects, yet quantitatively less pronounced.

## Method

### Subjects

A total of 600 subjects from a university sample completed the positive subscale of the Community Assessment of Psychic Experiences (CAPE; Stefanis *et al.* 2002). This questionnaire was completed voluntarily by first- and second-year undergraduate students to match them on social class and educational level.

Potential participants were identified when scoring above the 75th percentile of the distribution of individual positive CAPE scores for the high PS group, and below the 25th percentile for the comparison group (low PS). These subjects were invited to participate and were screened for exclusion criteria using a self-report checklist for healthy subjects, comprising the following points: (1) no personal history of neurological or psychiatric illness; (2) no family history of psychotic or neurological illness in first-degree relatives; (3) no use of illicit substances; and (4) no changes in overall level of functioning, including academic performance over the past 6 months. After receiving a complete description of study procedure, a total of 38 subjects were recruited (18 high PS, 20 low PS) and written informed consent was obtained from all of them. All subjects were paid for their participation. The study was approved by the Medical Ethical Committee of the University of Groningen.

### Instrument

The CAPE was used to measure positive schizotypal signs. This instrument was chosen on the basis of the following characteristics: (1) efficient assessment of subclinical schizotypal experiences in the general population (Hanssen *et al.* 2005), (2) good concurrent validity with interview-based measures (Konings *et al.* 2006), and (3) it was developed and standardized on a Dutch population. A detailed description of its psychometric properties and administration procedure can be found elsewhere (Stefanis *et al.* 2002).

In brief, this is a 42-item self-report questionnaire that measures the frequency of attenuated psychotic symptoms, on a four-point scale of 'never', 'sometimes', 'often' and 'nearly always'. Originally, the CAPE was based on a three-factor structure of positive, negative and depressive factors. For the purpose of the present study, we only used the scores on the positive factor because several studies have reported a relationship between the severity of positive psychotic symptoms and GMV in schizophrenia. In addition, all subjects completed the Beck Depression Inventory (BDI; Beck *et al.* 1996), which is a widely used, well-validated measure for depression, administered in our study to control for other psychiatric symptomatology that could act as confound for schizotypal signs (i.e. negative symptoms).

### MRI data acquisition

High-resolution MR images were acquired on a 3-T Philips Intera MR scanner (Philips Medical Systems, The Netherlands). Subjects were scanned with a T1-weighted 3D fast-field echo (FFE) sequence [repetition time (TR)=25 ms, echo time (TE)=4.6 ms, field of view (FOV)=260 mm, matrix=256 × 256, 160 contiguous axial slices of 1-mm thickness, voxel size = 1 × 1 × 1 mm.

### MRI data preprocessing

Structural images were pre-processed using optimized VBM implemented on the SPM5 software package (Wellcome Department of Cognitive Neurology, UK) running under Matlab 7.4 (The MathWorks, USA). VBM is a whole-brain, unbiased, semi-automated technique for characterizing regional cerebral differences in structural MR images (Ashburner & Friston, 2000; Good *et al.* 2001; Mechelli *et al.* 2005). Structural images were segmented to extract gray matter and then normalized to an asymmetric T1-weighted template in Montreal Neurological Institute (MNI) stereotactic space, in a recursive fashion. Image segmentation incorporated an intensity non-uniformity correction to account for smooth intensity variations caused by gradient distortions and different positions of cranial structures within the MRI coil (Ashburner & Friston, 2000). A further step was added to ensure that the total amount of gray matter in each voxel was conserved before and after spatial normalization (Good *et al.* 2001). This 'modulation' step involves multiplying the spatially normalized gray matter by its relative volume before and after spatial normalization. The resulting gray-matter images were finally smoothed with a 12-mm isotropic Gaussian kernel. Smoothing is required to compensate for the inexact

nature of spatial normalization and to maximize the chance that regional effects are expressed at a spatial scale where homologies in structural anatomy exist over subjects. After smoothing, each voxel represents the local average amount of gray matter in the region, the size of which is defined by the smoothing kernel.

### Statistical analysis

An analysis of covariance (ANCOVA) was designed by applying the general linear model (GLM) to compare the modulated gray-matter images of subjects with high and low positive PS. Global GMV, BDI scores and age were modeled as covariates of no interest to identify regionally specific differences that were not confounded by these variables. Global GMV was estimated using the total amount of gray matter in the gray-matter images obtained from segmentation, including the cerebellar gray matter.

Inferences were made using a statistical threshold of  $p < 0.05$  after false-discovery rate (FDR) correction for multiple comparisons across the whole brain. In addition to the whole-brain analysis, we performed six region-of-interest (ROI) analyses. The ROIs were defined on the basis of the reported stereotactic coordinates of ROIs from the study of SPD by Kawasaki *et al.* (2004) and from VBM reports in high-risk subjects (Pantelis *et al.* 2003; Borgwardt *et al.* 2007a). These included: (1) medial temporal structures (hippocampus, parahippocampus and surrounding area:  $x = -26$ ,  $y = -12$ ,  $z = -14$ ); (2) left inferior frontal gyrus ( $x = 36$ ,  $y = 18$ ,  $z = -4$ ); (3) insula (left:  $x = -40$ ,  $y = -26$ ,  $z = 16$ ; right:  $x = 42$ ,  $y = 12$ ,  $z = 3$ ); (4) superior temporal gyrus ( $x = 32$ ,  $y = 6$ ,  $z = -32$ ); (5) cingulate gyrus (anterior:  $x = -6$ ,  $y = 0$ ,  $z = 43$ ; posterior:  $x = 2$ ,  $y = -50$ ,  $z = 24$ ); and (6) precuneus ( $x = 2$ ,  $y = -52$ ,  $z = 52$ ). ROIs were defined using a sphere of radius 10 mm around the focus, using the Small Volume Correction (SVC) tool in SPM5. Significance was set at  $p < 0.05$ , FDR corrected.

For regions showing significant between-group differences, we extracted the individual GMVs for each participant and subjected them to correlation analysis (Pearson) with the scores on the positive factor of the CAPE questionnaire, in order to further explore the nature of their associations. To this end, we used the SPSS 16.0 statistical package for Mac (SPSS Inc., USA), with a two-tailed  $\alpha$  level of 0.05.

## Results

### Demographic and clinical results

Significant differences in age, BDI scores and global GMV were observed between the two study groups.

**Table 1.** Demographic and clinical characteristics, and global gray-matter volumes (GMVs) of study sample

Variable	Total sample ( <i>n</i> = 38)	Low positive PS ( <i>n</i> = 20)	High positive PS ( <i>n</i> = 18)	<i>t</i> value	<i>p</i> value
Age (years), mean (s.d.)	20.16 (2.33)	20.95 (2.69)	19.85 (1.49)	2.405	0.022
Sex, male/female	19/19	10/10	9/9	–	–
Handedness	Right	Right	Right	–	–
CAPE positive factor, mean score (s.d.), range	1.42 (0.35), 1.15	1.12 (0.04), 0.15	1.75 (1.15), 0.50	–16.650	0.000
BDI, mean score (s.d.)	4.11 (3.03)	2.46 (2.41)	5.95 (2.59)	–4.305	0.000
Global GMV, mean value (s.d.)	99 402.64 (26 548.67)	90 204.20 (26 078.20)	109 620.12 (23 744.22)	–2.390	0.022

PS, Psychometric schizotypy; s.d., standard deviation; CAPE, Community Assessment of Psychic Experiences; BDI, Beck Depression Inventory.

**Table 2.** Regions of gray-matter volume differences between subjects with high versus subjects with low positive psychometric schizotypy ( $p < 0.05$ , FDR corrected)

Area	Hemisphere	MNI coordinates of maximum significance			Size of cluster	<i>p</i> value	<i>z</i> value
		<i>x</i>	<i>y</i>	<i>z</i>			
PCC	Medial	2	–42	18	110	0.020	3.65
Precuneus	Medial	0	–54	44	107	0.042	2.60

PCC, Posterior cingulate cortex; FDR, false-discovery rate; MNI, Montreal Neurological Institute.

Hence, these three variables were entered in the statistical design as covariates of no interest to control for potential effects on between-group GMV differences. There were no group differences in gender or handedness (see Table 1).

There was a significant negative correlation between CAPE positive factor scores and age ( $r = -0.356$ ,  $p = 0.028$ ). Although none of the subjects in the study scored above the cut-off on the BDI, there was a significant correlation between this test and the CAPE positive factor ( $r = 0.615$ ,  $p < 0.001$ ). Thus, higher scores on positive PS were associated with younger age, and higher ratings of depression.

### VBM results: low PS versus high PS

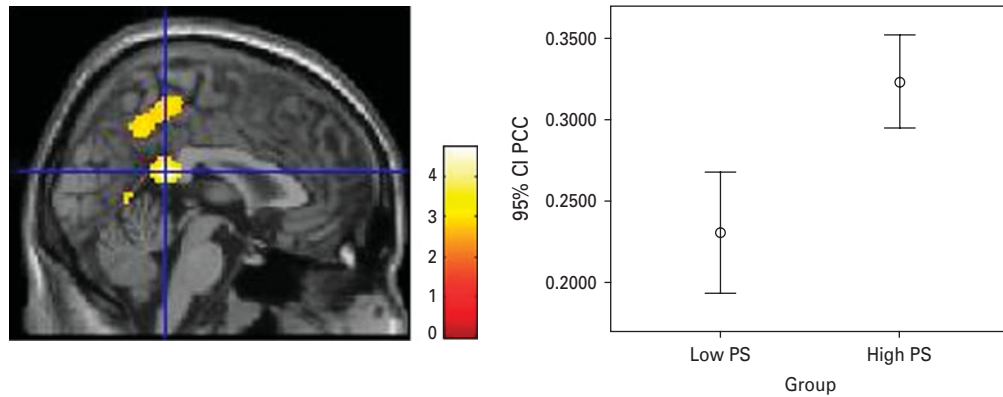
Global GMV correlated significantly with CAPE positive factor scores ( $r = 0.325$ ,  $p = 0.047$ ). A direct comparison between the high and the low PS groups confirmed larger global GMV in subjects with high positive PS ( $t$  score =  $-2.390$ ,  $p = 0.022$ ).

With regard to regional GMV, we detected two regions of greater volume in the high relative to the low positive PS group: the medial posterior cingulate cortex (PCC) and the precuneus (see Table 2, Figs 1 and 2). Conversely, there were no areas where volume

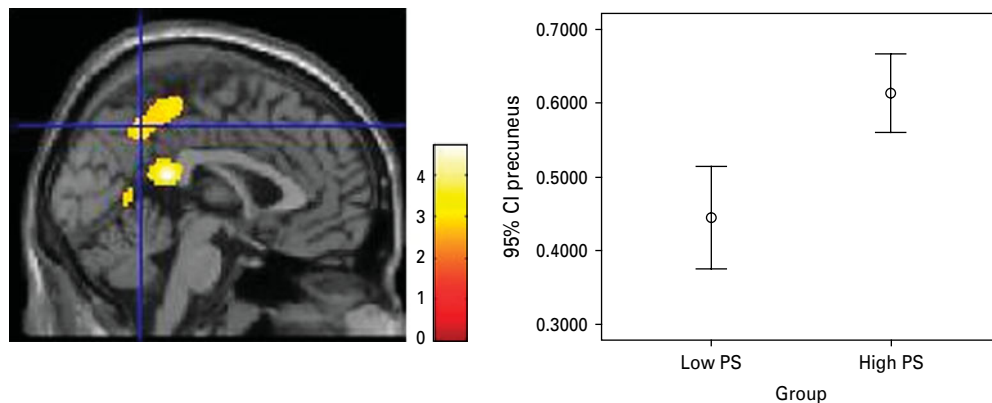
was significantly smaller in subjects with high positive PS. Finally, the GMV in each of these two regions was extracted and subjected to correlation analysis with the CAPE positive factor scores. Significant correlations were found between the CAPE positive factor and both the PCC ( $r = 0.503$ ,  $p = 0.001$ ) and precuneus ( $r = 0.484$ ,  $p = 0.001$ ) volumes. Cook's *D* test was applied to rule out the influence of potential outliers on the correlation. This correction strengthened the significance of the correlations in both cases (PCC:  $r = 0.604$ ,  $p < 0.001$ ; precuneus:  $r = 0.644$ ,  $p < 0.001$ ) (Fig. 3).

### Conclusions

The present study investigated GMV in positive PS. Using a series of ROI analyses, we examined the brain regions that have been previously implicated in volumetric studies of schizophrenia spectrum disorders. The approach used here showed significant global GMV differences between subjects with high compared to low positive PS, with high schizotypal subjects showing larger volume. We also found significant differences in focal GMV in the PCC and the medial precuneus. These global and regional MRI findings



**Fig. 1.** Increased gray-matter volume in the medial posterior cingulate cortex (PCC) in subjects with high scores on positive psychometric schizotypy (PS) relative to subjects with low scores, at a  $p$ -uncorrected level of 0.005. Between-group differences were considered significant at  $p < 0.05$ , false-discovery rate corrected.



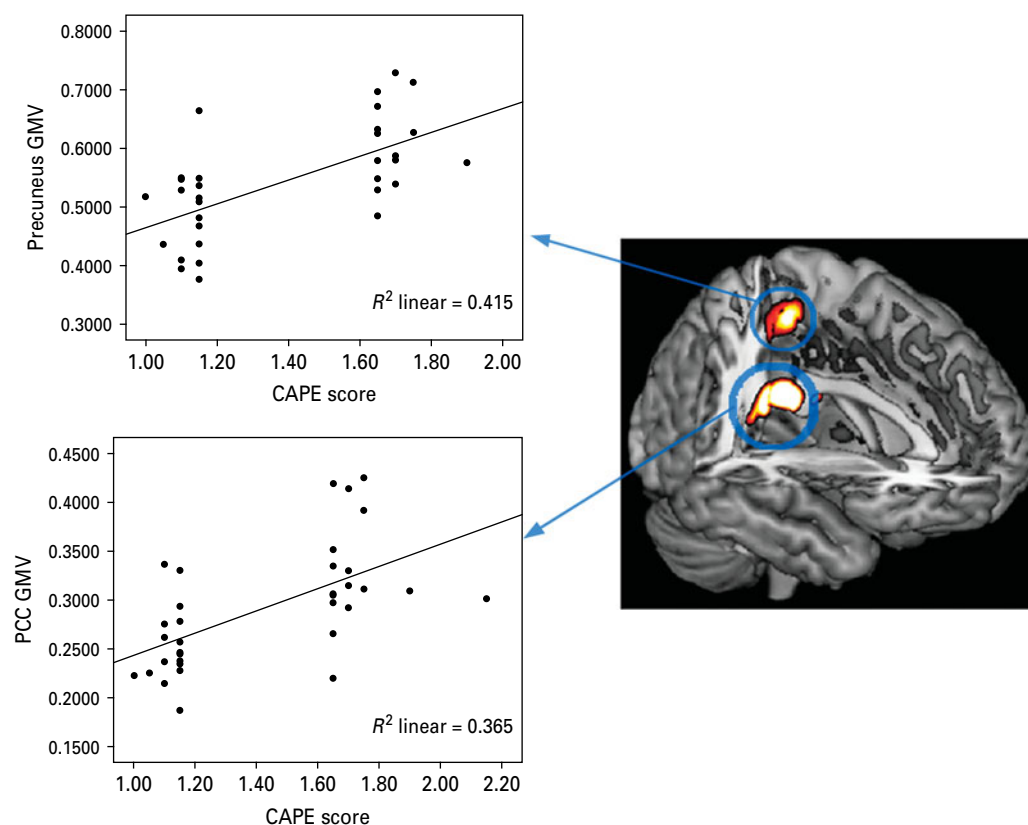
**Fig. 2.** Increased gray-matter volume in the medial precuneus in subjects with high scores on positive psychometric schizotypy (PS) relative to subjects with low scores, at a  $p$ -uncorrected level of 0.005. Between-group differences were considered significant at  $p < 0.05$ , false-discovery rate corrected.

cannot be attributed to differences in BDI scores or age as these variables were modeled as covariates of no interest in the statistical analysis.

To our knowledge, this is the first study to investigate brain morphology with VBM in subjects with high positive PS. We tested the hypothesis that alterations in GMV would be located within the same regions that are sites of abnormal GMV in ARMS, SPD and schizophrenia. Our results are consistent with this hypothesis, as the PCC had previously been implicated in structural MRI studies of chronic schizophrenia (Hulshoff Pol *et al.* 2001; Mitelman *et al.* 2005), first-episode schizophrenia (Kubiki *et al.* 2002; Job *et al.* 2003; Koo *et al.* 2008), early-onset schizophrenia (Sowell *et al.* 2000), and high-risk subjects (Pantelis *et al.* 2003; Borgwardt *et al.* 2007a,b). Moreover, most of these studies also reported abnormalities in the precuneus (Hulshoff Pol *et al.* 2001; Shapleske *et al.* 2002; Pantelis *et al.* 2003; Borgwardt *et al.* 2007a,b;

Zhou *et al.* 2007). Although these previous findings were of *reduced* GMV in these regions in schizophrenia and the ARMS, in the present study high positive PS was associated with relatively *greater* GMV in the PCC and precuneus.

Increases, rather than decreases, in GMV have been found in other schizophrenia spectrum disorders. Increased GMV has been described in first-episode schizophrenia patients with hallucinations compared to non-hallucinators in frontal and temporal regions (Shin *et al.* 2005). Furthermore, two studies have reported larger prefrontal volume in subjects with SPD compared to controls (Suzuki *et al.* 2005b; Hazlett *et al.* 2008), and relatively increased regional volumes have been found in ARMS subjects who later developed psychosis. Individuals who later transited to psychosis showed larger volumes in the left hippocampus (Phillips *et al.* 2002), in the parahippocampal, parietal and posterior temporal cortex, and also in the thalamus



**Fig. 3.** Areas of increased gray-matter volume (GMV) in subjects with high scores on positive psychometric schizotypy (PS) at a *p*-uncorrected level of 0.005. The scatterplots show the correspondent positive relationships between individual scores in PS [Community Assessment of Psychic Experiences (CAPE) positive factor] and GMV in the medial posterior cingulate cortex (PCC) and medial precuneus.

(Borgwardt *et al.* 2007b), the pituitary gland (Garner *et al.* 2005) and the cuneus (Pantelis *et al.* 2003), compared to those who did not transit to psychosis. The reason for relatively greater volumes in these regions is not yet understood, but it has been suggested they may reflect functional compensation for early disturbances in other brain regions (Kawasaki *et al.* 2004), or transient increases due to an active pathological process (Meisenzahl *et al.* 2008).

The precuneus, which is part of the parietal lobe, has been implicated in discriminating agency and, in patients with schizophrenia, in delusions of control (Sirigu *et al.* 1999; Blakemore *et al.* 2002). The cingulate cortex is thought to mediate cognitive and emotional impairments in patients with schizophrenia, although this seems to be more true of its anterior than its posterior portion (Baiano *et al.* 2007). Both the precuneus and PCC are key components of the 'default mode' network of the human brain (Cavanna & Trimble, 2006; Fransson & Marrelec, 2008). Patients with schizophrenia show aberrant functional connectivity within this network, which may contribute to the positive and negative symptoms of the disorder (Garritty *et al.* 2007).

The significant negative correlation between age and CAPE is consistent with research on self-reported experiences in non-clinical populations showing a reduction in the endorsement of such experiences as age increases (Van Os *et al.* 2000; Verdoux & Van Os, 2002). According to these studies, this could reflect an increased propensity of subjects at a younger age from the general population to endorse unusual ideas or strange beliefs (Verdoux & Van Os, 2002). In addition, CAPE and BDI scores were positively correlated, in keeping with previous findings of an association between symptoms of depression and the positive symptom dimension of schizotypy (Lewandowski *et al.* 2006). Nonetheless, we observed an effect of the positive psychotic-like experiences on GMV after controlling for the effect of age and BDI in the statistical analyses (between-group differences remained significant).

Finally, it has been proposed that schizophrenia could result from a disruption of brain maturation during adolescence (Rapoport *et al.* 1999; Thompson *et al.* 2001). Given that the average age of our participants was around 20 years, increased GMV in high PS subjects might reflect a delay in synaptic pruning

(Gotay *et al.* 2004). Moreover, increased global GMV has been described in other disorders of neurodevelopmental origin, such as autism (Palmen *et al.* 2004).

As in previous neuroimaging studies of other high-risk groups, the sample size in the present study was relatively small. Groups were formed with high and low scorers to allow consistency with previous literature on PS, which has typically compared behavioral performance between groups selected upon the same criterion (e.g. Langdon & Coltheart, 1999, 2001, 2004; Platek & Gallup, 2002; Jahshan & Sergi, 2007; Fernyhough *et al.* 2008). The distribution of schizotypy in non-clinical samples does not show a continuous normal distribution but a continuous half-normal distribution, with the majority of the population having very low values, although a significant proportion also has progressively higher values (Van Os *et al.* 2009). In addition, compared to other measures of schizotypal signs (e.g. Paranoia Scale, Launay-Slade Hallucination Scale), the CAPE comprises more 'pathological' items (e.g. does not tap on phenomena such as day-dreaming), so that very low scores are 'normal'. Thus, using average scorers would not be expected to significantly alter the present findings. However, future studies on PS including such control group should help expand our findings. Another potential limitation of the present study is that the subjects were recruited from a university sample, and caution should therefore be used when extrapolating the present findings to schizotypy in the general population. Nevertheless, this study demonstrated, for the first time, altered GMV in the PCC and precuneus in a group of subjects with high scores on positive PS, consistent with volumetric findings in these regions in schizophrenia spectrum disorders. These findings can be interpreted as correlates of the increased risk of schizophrenia in these subjects.

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## Declaration of Interest

None.

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